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CBER-00-012

Center for Biologics Evaluation and
Research
1401 Rockville Pike
Rockville MD 20852-1448

MAR - 1 2000

WARNING LETTER

Certified Mail
Return Receipt Requested

Glenn P. Lambert, MD, Chairman
Essex Institutional Review Board, Inc.
121 Main Street
Lebanon, NJ 08833

Dear Dr. Lambert:

During an inspection that concluded on July 22, 1999, Ms. Jean M. Kelahan, an investigator with the Food and Drug Administration (FDA), inspected Essex Institutional Review Board, Inc. (EIRB). The purpose of the inspection was to determine if EIRB's procedures for the protection of human subjects comply with FDA regulations, published in Title 21, Code of Federal Regulations, Parts 50 and 56 [21 CFR 50 and 56]. The inspection covered EIRB's initial and continuing review of clinical trials using Cultured Allogeneic Myoblasts, and Cyclosporin (Sandoz) in Myoblast Transfer Therapy for the treatment of muscular dystrophy, under BB-IND 5108, sponsored by the Cell Therapy Research Foundation (CTRF). The following clinical studies which we inspected were conducted by principal investigator Dr. Peter Law:

Protocol _____ Myoblast Transfer Therapy as an Experimental Treatment for Duchenne Muscular Dystrophy

Protocol _____ Whole Body Myoblast Transfer Therapy (MTT) as an Experimental Treatment for Duchenne Muscular Dystrophy (DMD) - Pivotal Trial

Protocol _____ Whole Body Myoblast Transfer Therapy as an Experimental Treatment for Becker Muscular Dystrophy

Protocol _____ Whole Body Myoblast Transfer Therapy (MTT) as an Experimental Treatment for Duchenne Muscular Dystrophy (DMD) - Expanded Access

Protocol _____ Single Patient Treatment using Whole Body Myoblast Transfer Therapy (MTT) as an Experimental Treatment for Duchenne Muscular Dystrophy (DMD)

Single Patient Treatment using Whole Body Myoblast Transfer Therapy (MTT) as an Experimental Treatment for Duchenne Muscular Dystrophy (DMD).

A copy of the list of Inspectional Observations (Form FDA 483) left with you at the end of the inspection is enclosed and is referenced below. We have reviewed Dr. Waggoner's letter dated August 16, 1999, which responded to the Form FDA 483, and our comments pertaining to EIRB's response follow. In addition to observations noted during the inspection, some items below are based on records collected and were not specifically itemized on the Form FDA 483. The deviations include, but are not limited to the following:

1. Failure to conduct adequate continuing review of research. [21 CFR 56.109(f)]

EIRB conducts continuing review inappropriately. The current system does not adequately ensure protection of research subjects. For example:

- a. EIRB received notification, on 3/31/98, that CTRF Protocol _____ was completed. The attachment to the final report summary form describes major changes and modifications to the protocol which did not receive EIRB review and approval, including changes in the:
- time interval between performance of upper body and lower body MTT therapy, study design,
 - time interval measurements for the efficacy parameters, eligible study subjects and donors,
 - number of cells injected,
 - number of injections made for each muscle site location,
 - muscle donor inclusion/exclusion criteria, and
 - subject informed consent form.

EIRB did not question why these changes were not submitted for review and approval prior to study implementation and completion or attempt to assess the impact of the changes to the study integrity and the research subjects.

- b. A one year extension of Protocol _____ during 1995 & 1996 was granted without updated study status information on the total number of study subjects enrolled, dropped, or discontinued for any reasons, or the review of any report of adverse events submitted by Dr. Law.

Your response to Form FDA 483, Item No. 4, adequately addressed the item 1b. We note that the documentation for updated study status information included in your response was not provided to our investigator during the inspection.

- c. It appears that EIRB approved Protocol _____ prior to receiving a letter requesting review of the clinical protocol from CTRF. No submission letter was observed in the EIRB study file from CTRF to EIRB for the review of Protocol _____ until 2/10/99. However, the study protocol was stamped "approved Jan 11, 1999." Please explain how this occurred.

2. Failure to fulfill requirements for expedited review. [21 CFR 56.110]

Study protocols_____ are subsequent treatment protocols for the administration of this product in vulnerable children. The protocol describes MTT to involve anesthesia and multiple injections which could temporarily or permanently cause muscle injury to vulnerable children. These protocols are neither research involving "minimal risk" nor simply "minor changes" in previously approved research. These two protocols were approved via "Chairman's Review" without any review or discussion of the study protocols by the full board. In addition, there is no documentation to demonstrate that the approvals were reported to the full board for review and discussion.

Your response to the Form FDA 483, Item No. 5, did not adequately address this issue. Please provide additional information and documentation to support that these two protocols were reviewed and discussed by the members of EIRB during the board meeting mentioned in your response. Is there documentation from the meeting minutes to show that these two protocols were reviewed and discussed by the board? Were there any concerns raised during the board meeting discussion of these two protocols?

Please describe the EIRB procedures and corrective measures you will implement to meet the regulatory requirements for expedited review.

The most recent list of categories of research that may be reviewed by the institutional review board through an expedited review procedure is available on the World Wide Web at <http://www.fda.gov/ohrms/dockets/98fr/110998b.txt>.

3. Failure to prepare adequate documentation of IRB activities. [21 CFR 56.115 (a)(3)]

- a. On 5/21/96 CTRF submitted to EIRB recognition of _____ as a facility available for extended treatment, should the need arise. No documentation was found indicating the IRB of record, either Essex IRB or the St. Francis Hospital IRB.
- b. The EIRB Chairman, Dr. Waggoner, conducted a site visit of Dr. Law's study site in March of 1999. No report was prepared to inform the full board of the outcome or issues resulting from the site visit or the status of Dr. Law's clinical studies regarding compliance with FDA regulations and IRB policies.

Your response to the Form FDA 483, Item No. 2, did not adequately address this deviation. What procedures will be established to ensure that the result or outcome of a study site visit will be reported to the full board for discussion? How will concerns be raised and addressed? How will EIRB determine if the investigator's study is in compliance with FDA regulations and IRB policies following a site visit? How will you ensure that community attitudes will be considered?

4. Failure to prepare and follow detailed written procedures for conducting the review of research, including periodic review. [21 CFR 56.108 (a) and (b), and 56.115(a)(6)]

Requirements for full board review as specified on pages 4-5 of the EIRB Submission Guidelines are not being followed. For example:

- a. Review of study records for Protocol _____ revealed that there is no documentation of a signed FDA Form 1572 for Dr. Law or Dr. Holcomb, as required by the EIRB Submission Guidelines.
- b. There is no curriculum vitae (c.v.) on file for the co-investigator, Dr. Prasad Duggaralia, for Protocol _____ that was approved by the EIRB on 3/3/99.
- c. No advertising or promotional labeling information (e.g., newspaper, flyers, video, radio, e-mail, web site information) was submitted to the EIRB for review and approval in any of the 6 study files inspected. FDA is aware of various promotional materials distributed by CTRF including promotion of MTT on the internet, a video tape entitled "Race for Life," and other media interview materials. There is no EIRB documentation regarding an inquiry or a request for Dr. Law to submit promotional and advertising materials for the studies.
- d. The EIRB continuing review reporting forms do not capture the study completion date. For example, the final report for Protocol _____, approved by EIRB on 4/6/98 did not identify the date that the study was actually completed. Without the actual date of study completion, the EIRB cannot be assured that the site reported within the required 30 days following project completion, as specified in the EIRB Combination Report Form.

Your response to Form FDA 483, Item No. 4, adequately corrected part 4d of the above concerns. Subsequent to the inspection, we note that the EIRB Standard Report Form for extensions, final reports, or requests for increase in study subjects has been revised to include the date of study completion.

5. Failure to accurately record the attendance and voting by IRB members. [21 CFR 56.115(a)(2)]

EIRB procedures for documenting minutes of the board meetings should be revised to conform with regulations, as evidenced by the following examples:

- a. The Categories of IRB Action section, page 12 of the EIRB Submission Guidelines Procedure, includes the statement "If no voting score is mentioned in meeting minutes, the approval was unanimous." This statement is not in compliance with FDA IRB regulations or page 15 of the EIRB Submission Guidelines, which state "Minutes of EIRB meetings shall be taken in sufficient detail to show the following: Attendance at meetings; actions taken by the EIRB; the vote on these actions including the number of members voting for, against, or abstaining..."

- b. According to the meeting minutes reviewed during the inspection, EIRB granted approvals on the following protocols: Protocol _____ on 1/11/94, Protocol _____ on 4/22/96 and Protocol _____ on 2/22/99. These minutes do not indicate the number of members voting for, against, or abstaining, or if the vote was unanimous, or if at least 80% of board members present were in favor of approval, as required in the EIRB's procedure. Additionally, the EIRB minutes for the approval of Protocol _____ do not identify who the alternate member replaced or if that member voted or not.
6. **Failure to ensure that the additional requirements of informed consent are fulfilled. [21CFR 50.25 (b) (3)].**

The EIRB did not perform the necessary review to determine if cost recovery had been authorized by FDA and to ensure that consent forms for each of Dr. Law's IRB approved studies fully disclosed the amount to be charged for MTT treatment.

- a. For the six clinical protocols reviewed and approved for Dr. Law, EIRB did not perform the necessary review to ensure that charges incurred by study subjects for MTT treatment received FDA authorization. FDA informed consent regulations require the consent document to include any additional costs to the subjects that may result from participation in the research.
- b. The final informed consent form version (dated 2/24/99) for Protocol _____ approved by EIRB on 3/3/99, and the final informed consent form (dated 3/12/99) for Protocol _____ approved by EIRB on 3/23/99, did not describe the cost associated with MTT treatment.
- c. EIRB approved the revised 5/17/96 informed consent form for Protocol _____ on 4/22/96 without any mention of the cost of MTT. EIRB made no inquiry into the costs incurred by subjects receiving MTT treatments, although costs _____ were specified in the proposed 11/10/95 informed consent form for Study _____.
- d. EIRB had no documentation to show whether it inquired further with CTRF regarding costs associated with MTT therapies described in the patient informed consent final approved version dated 3/4/99 for Protocol _____. The Financial Incentive and Costs section of the EIRB approved Patient Informed Consent included the statement "Any costs associated with MTT have been covered in prior discussions. If you have any questions concerning these costs, please ask." This same statement was also noted in the same section of the Patient Consent Form (Rev. 4-29-99) for Protocol _____ approved by EIRB on 5/3/99. There was no FDA authorization for cost recovery in effect in 1999 at the time those protocol versions were approved.

Your response to Form FDA 483, Item No. 1, did not adequately address the above concerns. The patient consent form for each protocol needs to clearly state the amount the patient will be charged or the amount of reimbursement being requested for MTT treatment. EIRB should ensure that the subjects are fully informed about what the cost will be for MTT treatment and that the amount

being charged complies with the cost recovery provisions that receive FDA approval.

Please describe in detail the additional procedures and measures you plan to implement to ensure (a) that when study participants are being charged, the cost to be recovered for an investigational product is clearly disclosed in the patient consent form for each study protocol, and (b) that the amount being charged has received agency authorization. EIRB should obtain cost recovery information, e.g, copy of the FDA authorization letter, from the sponsor or investigator as part of your IRB review responsibilities.

7. Failure to fulfill the requirements of informed consent. [21 CFR 50.20]

- a. Patient consent forms for some myoblast donors contain exculpatory language through which the subject is made to waive or appear to waive legal rights. Such language is clearly prohibited.
- b. Patient consent forms are not in a language understandable to all study subjects or their representative. For example:

The protocol and patient consent forms for Protocol ~~_____~~ 3/3/99, were reviewed and approved by the EIRB Chairman on 3/4/99. The subjects treated were six-year old Spanish twin boys. Review of IRB records revealed that the patient and donor consent forms were not translated into language understandable to the Spanish family.

Your response to the FDA 483, Item No. 3, did not adequately address this deviation. The study subjects were not considered to be "unexpectedly encountered." The long preparatory time necessary to grow cells for MTT and to perform the initial testing and screening allowed more than ample opportunity for the translation of the informed consent document. As required by the regulations, non-English speaking subjects need to be provided with a consent document accurately translated in their language.

This letter is not intended to be an all-inclusive list of deficiencies that may exist with the EIRB. The EIRB is responsible for adhering to each requirement of the law and applicable regulations.

Based upon the demonstrated deficiencies in organizational guidelines, operational procedures, record-keeping practices, and demonstrated deficiencies regarding continuing review and informed consent issues, it appears that your procedures are inadequate to protect the rights and welfare of human subjects of research. Failure to make adequate corrections may result in regulatory action being initiated by the Food and Drug Administration. As described in section 56.120 and 56.121 of the regulations, these actions include withholding approval of new studies, direction that no new subjects be added to ongoing studies, termination of ongoing studies, notification of State and Federal regulatory agencies, and the initiation of regulatory proceedings for disqualification of your IRB.

Please notify this office in writing, within 15 working days of receipt of this letter, of the specific steps you have taken or plan to take to bring the procedures of your Institutional

Review Board into compliance with FDA requirements. If corrective action cannot be completed within 15 working days, state the time within which the corrections will be completed.

Your file will remain open until we receive your response and it is deemed adequate. The website to the *FDA Information Sheets* (<http://www.fda.gov/oc/oha/IRB/toc.html>) is provided to assist you in implementing the changes necessary to bring the IRB into compliance with applicable standards. Appendix H of the FDA Information Sheets provides guidance to ensure that all required elements are included in your written procedures.

Should you have any questions or comments about this letter or any aspects of the operation and responsibilities of a institutional review board, you may contact Dr. J. Lloyd Johnson, Regulatory Review Officer, Bioresearch Monitoring Branch, Division of Inspections and Surveillance, at (301) 827-6221.

Your response should be sent to the following address: FDA, Center for Biologics Evaluation and Research, Office of Compliance and Biologics Quality, HFM-600, 1401 Rockville Pike, Rockville, Maryland 20852-1448.

Sincerely,



Steven A. Masiello
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation
and Research

Enclosure:

Form FDA 483, Inspectional Observations, dated 7/22/99

cc:

William C. Waggoner, Ph.D., FAACT
Essex Institutional Review Board, Inc.
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